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FACTORS DETERMINING BONE MINERAL DENSITY AND TRABECULAR BONE SCORE IN YOUNG WOMEN WITH HYPERANDROGENISM

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Abstract

TBS seems to be more a reliable determinant of bone quality in patients with this condition, since contrary to BMD, it is less susceptible to confounding effects of altered hormonal and metabolic parameters.

Keywords: bone mineral density, hyperandrogenism

Peak bone mass (PBM) achieved during puberty is a key determinant of bone quality in adult women, especially after menopause [1]. PBM is influenced by an array of factors, both extrinsic and intrinsic [2]. Among the latter, particularly important role is played by

hormonal factors, especially endocrine activity of the ovaries [3]. Hormonal disorders in the adolescence result not only in delayed puberty, but also in general disruption of homeostasis, including impairment of bone formation. A model example of a hormonal disorder with such complex effects is hyperandrogenism, during the course of which relative, and later also absolute, deficiency of estrogens is reflected not only by impaired osteogenesis, but also by general endocrine disruption and resultant changes in metabolic profile [4]. One consequence of excess androgen synthesis is change in the distribution of adipose tissue to android one, and a shift in its secretory profile to that typical for visceral fat [5]. Recent evidence suggests that these changes may also exert an unfavorable effect on bone mineralization [6].

Until recently, either in research or in everyday clinical practice, quality of the bone has been assessed on the basis of bone mineral density (BMD) determined densitometrically by means of dual energy X-ray absorptiometry (DEXA) [7]. However, results of recent studies imply that BMD determined with this method is not an independent predictor of osteoporotic fractures; moreover, this parameter can be biased in subjects with extremely low or high body weight [8,9]. These findings resulted in development of more accurate marker of bone microarchitecture, trabecular bone score (TBS), a measure extracted digitally from densitometric images [10].

Both our own experiences and results of previous studies imply that BMD in women with impaired ovarian function may be modulated by a plethora of hormonal and metabolic parameters; this may negatively affect diagnostic accuracy of BMD as a measure of subclinical bone depletion and fracture risk. The aim of this study was to determine which hormonal and metabolic parameters exert a significant effect on BMD in women with hyperandrogenism, and to verify if these factors also influence TBS, a marker of bone microarchitecture used increasing in densitometric studies.

Methods

Patients

The study, conducted in 2013-2015, included 213 women with hyperandrogenism, treated at the Department of Endocrinology, Metabolic and Internal Diseases, Pomeranian Medical University in Szczecin (Poland). Age of the study subjects ranged between 19 and 37 years (mean 27.08±4.33). The analysis included all patients treated at our clinic during the analyzed period, who satisfied the following inclusion criteria: 1) caucasian women not taking medicines on a regular basis, without material abnormalities in physical examination, and lack of exclusion criteria. The exclusion criteria were: 1) positive interview for chronic diseases

and endocrinopathy (polycystic ovary syndrome, diabetes mellitus, thyroid disease, diabetes mellitus, hypercortisolemia, gastrointestinal disease, nephropathy and diseases affecting bone mineralization).

Ethics

Protocol of the study was granted approval from the Local Bioethics Committee at the Pomeranian Medical University in Szczecin (decision no. KB-0012/115/15 of 16 November 2015), and written informed consent was sought from all the study subjects or their legal guardians in the case of underage participants.

Basic procedures

Upon history taking and routine clinical examination, anthropometric measurements (body weight and body height) were taken in each study subjects, and body mass index (BMI) value was calculated.

Laboratory parameters

The list of determined endocrine parameters included concentrations of androstenedione, dehydroepiandrosterone (DHEA), free testosterone and sex hormone-binding globulin (SHBG) – used to calculate free androgen index (FAI), 17-hydroxyprogesterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, prolactin at the baseline (PRL 0') and at 60 min of metoclopramide challenge (PRL 60'), thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), adrenocorticotropic hormone (ACTH), cortisol, as well as the levels of glucose and insulin prior to oral glucose tolerance test (75 g, OGTT) and after 60 and 120 min of the test. All parameters were determined using conventional methods, electrochemiluminescence immunoassay (ECLIA) for insulin, estradiol, LH, FSH, testosterone, SHBG, cortisol, ACTH, TSH, fT3, fT4, PRL, 17-hydroxyprogesterone and DHEA, immunoenzymatic assay (ELISA) for androstenedione, and hexokinase method for glucose.

Determination of bone mineral density and trabecular bone score

BMD of all the study subjects was determined both for the lumbar spine (L2-L4) and entire skeleton by means of dual-energy X-ray absorptiometry (DEXA, GE Lunar Prodigy Advance, Madison, WI, USA, with enCORE software version 8.8). The results were expressed as absolute values (g/cm^2) and as z-scores. TBS values of the same lumbar vertebrae were determined based on DXA images using dedicated analysis software (TBS I Nsight, version 2.1.2.0, Medimaps, Mérignac, France).

Determination of adipose tissue distribution and volume

Quantitative body composition, i.e. overall volume of body fat, volumes of android and gynoid fat, were determined by means of DEXA whole body scan (GE Lunar Prodigy Advance, Madison, WI, USA) using CoreScan ^{TM} H8801CP and Body Composition software packages provided by the manufacturer.

Statistical analysis

Normal distribution of continuous variables was verified with Shapiro-Wilk test and their statistical characteristics were presented as arithmetic means, standard deviations (SD), medians, lower and upper quartiles. Power and direction of relationships between pairs of continuous variables were estimated on the basis of Spearman's coefficients of rank correlation (R). Parameters that showed significant ($p \leq 0.05$) or close to statistical significance ($p \leq 0.1$) associations with dependent variables (TBS or BMD) were included in multiple linear regression models to identify independent predictors of these variables. All calculations were carried out with Statistica 10 software (StatSoft, USA).

Results

Detailed characteristics of the study subjects are presented in Table 1.

TBS correlated positively with both BMD ($R=0.334$, $p<0.001$) and BMD z-score ($R=0.263$, $p<0.001$). Furthermore, statistically significant positive correlations were found between TBS, BMI, overall volume of adipose tissue, volume of gynoid fat and TSH concentration. In turn, BMD correlated positively with age, BMI, volume of adipose tissue overall, volumes of both android and gynoid fat, fasting concentration of insulin, estradiol level and FAI. Moreover, an inverse correlation was found between BMD and SHBG concentration (Table 2).

Multivariate regression analysis demonstrated that TBS correlated positively with volume of gynoid fat and BMI, and showed an inverse correlation with total adipose tissue volume. Resultant regression model was statistically significant but explained only ca. 14% of variance within TBS ($R^2=0.138$, $p<0.0001$; Table 3). The only independent predictor of BMD identified on multivariate regression analysis was BMI. Also this model, despite statistical significance, explained only slightly above 16.5% of variance within the dependent variable ($R^2=0.167$, $p<0.001$; Table 4).

Discussion

This study demonstrated that BMD and TBS in women with hyperandrogenism are determined by different factors. BMI turned out to be the only independent predictor of BMD. Indeed, results of early studies suggested a positive correlation between body weight and bone mineralization, and this association was explained by a stimulatory effect of greater mechanical load on osteogenesis [11]. However, further research demonstrated that bone mineralization is determined by fat mass, rather than by total body weight or BMI [12].

Further discovery that adipose tissue is not merely a passive lipid reservoir, but disseminated endocrine gland with region-specific profiles of secreted substances, provided better insight in this phenomenon [13]. According to literature, gynoid fat, i.e. subcutaneous tissue accumulated around hips, breasts and thighs, synthesizes primarily pro-osteogenic and anti-osteolytic factors, such as adiponectin, leptin and aromatase [14-16]. In contrast, visceral adipose tissue, and probably also android (abdominal) fat, are sources of compounds that promote bone resorption, such as proinflammatory cytokines (TNF-alpha and IL-6) [17,18] and cell adhesion molecules (sICAM1 and E-selectin) [19,20]. Our data on independent predictors of TBS are consistent with these findings. Multivariate analysis of regression demonstrated that TBS in our study subjects correlated with their BMI and gynoid fat volume, and showed an inverse correlation with total volume of adipose tissue. The latter observation is an indirect proof for an inverse correlation between TBS, visceral and android fat contents.

Univariate analysis demonstrated, that aside from its independent predictors mentioned above, i.e. BMI, total volume of adipose tissue and gynoid fat volume, TBS correlated with only one parameter, TSH level. Theoretically, TSH might exert an indirect pro-osteogenic effect mediated via triiodothyronine (T3), as higher levels of the latter were recently shown to be associated with better qualitative characteristics of the bone [21]. However, such mechanism is unlikely, since we neither found a significant correlation between fT3 and TBS or BMD, nor THS proved to be an independent predictor of bone architecture on multivariate analysis. It cannot be excluded that the positive correlation between TSH and TBS was mediated by leptin since in one previous study, this pro-osteogenic adipokine synthesized in subcutaneous (in particular gynoid) fat was shown to correlate positively with TSH level [22]. Under such assumption, women with larger volumes of gynoid fat would synthesize more leptin, and the latter would exert independent effects on TSH metabolism and bone quality.

The number of factors that influenced BMD of our study subjects on univariate analysis was markedly higher than in the case of TBS. Aside from BMI, adipose tissue volume overall, gynoid and android fat volumes, BMD also correlated positively with fasting insulin, estradiol level and FAI, and showed an inverse correlation with SHBG concentration. None of these factors turned out to be an independent predictor of BMD on multivariate analysis, which implies that they were all linked to excess body weight and/or adiposity, rather than to bone mineralization. However, a large body of evidence suggests that all these parameters may also influence BMD directly. Estrogen deficiency is a well-established risk factor for bone loss [23-25]. Skeletal demineralization may also result from preferential

binding of androgens by SHBG and lack of their further conversion to estrogens [26-28]; this mechanism would explain why BMD in our study subjects correlated inversely with BMD and increased with FAI values. Finally, insulin was previously shown to stimulate differentiation of osteoblasts, probably via upregulation of osteocalcin [29-31].

Taken altogether, these findings imply that TBI may be a more reliable measure of bone quality in patients with hyperandrogenism than BMD. First, the results of multivariate analysis for TBS are consistent with published data on the biological role of adipose tissue in bone metabolism, whereas the results for BMD are quite conflicting. Second, the results of univariate analyses imply that contrary to BMD, TBS is less susceptible to confounding effects of other hormonal and metabolic parameters that may be substantially altered during the course of hyperandrogenism.

One principal limitation of this study is its retrospective character, due to which we were unable to exclude potential effects of additional laboratory parameters, such as leptin. Furthermore, our analysis was not adjusted for all potential determinants of bone quality, as shown by low R^2 values for both multivariate models. Other factors with established influence on bone properties are diet, physical activity, sunlight exposure and concomitant medications [32-35]. Finally, our study did not include a control group. Nevertheless, we hope that due to appropriate selection of statistical methodology (analysis of correlation and regression, rather than intergroup comparisons) and large sample size, the hereby presented findings are reliable; this assumption seems to be supported by their substantial consistency with published evidence.

Conclusions

TBS seems to be more a reliable determinant of bone quality in patients with this condition, since contrary to BMD, it is less susceptible to confounding effects of altered hormonal and metabolic parameters.

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Table 1. Clinicodemographic characteristics of the study subjects.

Variable	Mean	SD	Median	Lower quartile	Upper quartile
Age (years)	27.08	4.33	27.00	24.00	30.00
BMI (kg/m^2)	25.60	5.82	23.80	20.90	30.00
Fat overall (cm^3)	37.69	8.65	37.50	31.20	44.90
Android fat (cm^3)	41.14	12.63	42.70	31.30	51.60
Female fat (cm^3)	42.98	7.37	43.00	38.20	48.10
BMD (g/cm^2)	1.23	0.13	1.24	1.15	1.32
z-score	0.23	0.98	0.30	-0.40	1.00
TBS	1.38	0.09	1.38	1.32	1.43
Glucose 0' (mg/dl)	86.65	9.72	87.00	81.00	92.00
Insulin 0' (µIU/ml)	12.61	10.93	9.90	6.72	14.52
Glucose 60' (mg/dl)	114.43	36.21	112.90	87.20	134.20
Insulin 60' (µIU/ml)	88.28	72.79	65.78	42.22	106.40
Glucose 120' (mg/dl)	93.69	28.53	92.00	73.00	109.00
Insulin 120' (µIU/ml)	58.78	60.80	37.05	24.22	66.20
Androstenedione (ng/ml)	3.94	1.91	3.60	2.85	4.78
DHEA (µg/ml)	260.07	125.48	254.00	178.00	325.00
Testosterone (ng/ml)	0.50	0.22	0.48	0.36	0.62
SHBG (nmol/l)	56.11	45.98	45.50	28.34	70.70
FAI	5.29	5.18	3.94	2.07	6.46
17-hydroxyprogesterone (ng/ml)	1.17	0.65	1.10	0.76	1.47
LH (mIU/ml)	9.02	7.66	6.93	4.74	11.15
FSH (mIU/ml)	6.13	5.75	5.57	4.59	6.71
Estradiol (pg/ml)	69.42	81.71	45.34	32.61	70.49
PRL 0' (ng/ml)	20.11	24.06	16.65	11.20	22.40
PRL 60' (ng/ml)	166.18	73.81	157.80	121.70	189.80
TSH (µIU/ml)	2.40	3.50	1.81	1.31	2.83
fT3 (pg/ml)	3.05	0.35	2.95	2.80	3.34
fT4 (ng/dl)	1.44	1.80	1.23	1.12	1.33
Cortisol (µg/dl)	16.63	6.26	15.75	12.40	20.19
ACTH (pg/ml)	34.41	47.84	26.49	19.42	38.00

Table 2. Spearman's coefficients of rank correlation (R) between trabecular bone score (TBS) and bone mineral density (BMD) in lumbar spine and other clinicodemographic characteristics of the study subjects.

Explanatory variables	TBS		BMD (g/cm^2)	
	R	p	R	p
Age (years)	0.024	0.728	0.153	0.026
BMI (kg/m^2)	0.282	<0.001	0.394	0.000
Fat overall (cm^3)	0.175	0.012	0.284	0.000
Android fat (cm^3)	0.136	0.061	0.290	0.000
Female fat (cm^3)	0.199	0.004	0.208	0.002
Glucose 0' (mg/dl)	0.017	0.817	0.047	0.509
Insulin 0' (µIU/ml)	-0.010	0.891	0.173	0.016
Glucose 60' (mg/dl)	-0.007	0.926	0.078	0.289
Insulin 60' (µIU/ml)	-0.059	0.432	0.059	0.424
Glucose 120' (mg/dl)	-0.039	0.595	0.064	0.380
Insulin 120' (µIU/ml)	-0.058	0.427	0.058	0.428
Androstenedione (ng/ml)	-0.066	0.341	-0.038	0.585
DHEA (µg/ml)	-0.046	0.509	0.046	0.503
Testosterone (ng/ml)	-0.032	0.648	0.072	0.295
SHBG (nmol/l)	-0.072	0.298	-0.212	0.002
FAI	0.044	0.534	0.192	0.006
17-hydroxyprogesterone (ng/ml)	-0.020	0.770	0.047	0.492
LH (mIU/ml)	-0.029	0.672	-0.048	0.487
FSH (mIU/ml)	0.016	0.823	-0.093	0.175
Estradiol (pg/ml)	-0.099	0.154	0.180	0.008
PRL 0' (ng/ml)	-0.043	0.541	0.076	0.267
PRL 60' (ng/ml)	-0.059	0.398	0.054	0.429
TSH (µIU/ml)	0.157	0.027	-0.065	0.359
fT3 (pg/ml)	-0.147	0.114	-0.014	0.884
fT4 (ng/dl)	0.054	0.458	0.092	0.205
Cortisol (µg/dl)	0.084	0.351	0.099	0.263
ACTH (pg/ml)	0.012	0.893	0.049	0.592

Table 3. Determinants of trabecular bone score (TBS) in lumbar spine of women with hyperandrogenism – results of multivariate analysis of regression.

Explanatory variable	b*	SE for b*	b	SE for b	p
BMI (kg/m^2)	0.447	0.126	0.007	0.002	0.001
Fat overall (cm^3)	-0.716	0.228	-0.008	0.002	0.002
Female fat (cm^3)	0.638	0.174	0.008	0.002	<0.001
TSH (μIU/ml)	0.034	0.069	0.001	0.002	0.619

Table 4. Determinants of bone mineral density (BMD) in lumbar spine of women with hyperandrogenism – results of multivariate analysis of regression.

Explanatory variable	b*	SE for b*	b	SE for b	p
Age (years)	0.122	0.072	0.003	0.002	0.091
BMI (kg/m^2)	0.401	0.132	0.008	0.003	0.003
Fat overall (cm^3)	-0.086	0.341	-0.001	0.005	0.801
Android fat (cm^3)	0.117	0.239	0.001	0.002	0.626
Female fat (cm^3)	-0.008	0.182	<-0.001	0.003	0.967
Insulin 0' (μIU/ml)	-0.130	0.085	-0.001	0.001	0.127
SHBG (nmol/l)	-0.020	0.080	<-0.001	<0.001	0.804
FAI	-0.070	0.086	-0.002	0.002	0.418
Estradiol (pg/ml)	0.083	0.070	<0.001	<0.001	0.237